Do Nutritional Supplements Lower the Risk of Stroke or Hypertension?

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Between 1986 and 1991, 29,584 persons took part in a randomized nutritional intervention trial in Linxian, China, an area whose residents had chronically low intakes of several nutrients and high rates of esophageal and gastric cardia cancer as well as stroke. Using a one-half replicate of a 2^4 factorial design, we randomized individuals to one of eight groups which received combinations of four supplements: retinol and zinc (factor A); riboflavin and niacin (factor B); vitamin C and molybdenum (factor C); and beta-carotene, alpha-tocopherol (vitamin E), and selenium (factor D). Deaths that occurred during 5 years of supplementation were ascertained and classified according to cause. At the end of the supplementation period, we measured blood pressure readings and determined the prevalence of hypertension. Participants who received factor D had reductions in total mortality (9%) and total cancer mortality (13%). These individuals also had the largest reduction in stroke mortality (relative risk = 0.91; 95% confidence interval = 0.76–1.07). End-of-trial hypertension, however, was not less prevalent among those receiving factor D. Our findings contrast with the larger reductions in stroke death and hypertension found in a parallel trial of Linxian subjects with esophageal dysplasia who received a multivitamin/mineral supplement, suggesting an effect largely derived from nutrients other than those received in the present study. (Epidemiology 1998;9:9–15)

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Stroke disease is the second leading cause of death in Linxian, a county in north central China with one of the world's highest rates of esophageal/gastric cardia cancer.[1] The determinants of stroke in Linxian and other parts of China are not well known, but dietary constituents, including low vitamin and mineral intake, may be involved. As part of a randomized trial to evaluate the effectiveness of supplementation with each of four combinations of nutritional supplements on esophageal/gastric cardia cancer, we obtained information on all deaths, including those from stroke. In addition, blood pressure was measured before and after the vitamin/mineral interventions. We have previously reported a beneficial effect of the supplement that contained beta-carotene, vitamin E, and selenium (factor D) on reducing total mortality, cancer mortality, and cancer incidence. Herein, we report the effects of the supplements on stroke mortality and on the prevalence of hypertension at the end of the intervention. We also examine the relation of pretreatment factors, such as sex, body mass index, alcohol intake, and smoking, to stroke mortality. The study was conducted in conjunction with a smaller trial in Linxian that tested a single multivitamin/mineral supplement containing 26 nutrients. In that trial, supplement users had decreased stroke mortality and hypertension, with the effect most pronounced among men.[2]

Methods

Elsewhere, we have given[3,4] a detailed description of the design, methods of conduct, and primary endpoint analyses of the Linxian General Population Trial. In brief, 29,584 adults ages 40–60 years from four Linxian communes were randomly assigned to receive one of eight vitamin/mineral combinations. Before enrollment, we obtained informed consent from each participant, and throughout the trial, human subject protection procedures in accord with those prescribed by the National Institutes of Health and the Chinese Academy of Medical Sciences were enforced. We excluded individuals with a history of cancer or debilitating diseases. As shown in Table 1, the treatment groups were defined by the following eight combinations of four different vitamin/mineral combinations, which we designate as factors A, B, C, D: AB, AC, AD, BC, BD, CD, ABCD, or placebo. This process resulted in half of the participants

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TABLE 1. Nutrient Combinations and Doses Used in the Treatment Factors

	Dose
Factor A	
Vitamin A (retinol palmitate) (IU)	10,000
Zinc (zinc oxide) (mg)	45
Factor B	
Riboflavin (mg)	5.2
Niacin (mg)	40
Factor C	
Ascorbic acid (mg)	180
Molybdenum (yeast complex) (μg)	30
Factor D	
Beta-carotene (mg)	15
Selenium (selenium yeast) (μg)	50
Alpha-tocopherol (mg)	60

TABLE 2. Baseline Characteristics by Sex

Female (%)	55
Drinking* (%)	10
Smoking† (%)	0.20
Age‡ (years)	51 (44–58)
Systolic blood pressure‡ (mmHg)	130 (110–140)
Diastolic blood pressure‡ (mmHg)	80 (70–90)
Body mass index‡	21.9 (20.3–23.7)
Male (%)	45
Drinking (%)	40
Smoking (%)	67
Age‡ (years)	53 (45–60)
Systolic blood pressure‡ (mmHg)	120 (110–140)
Diastolic blood pressure‡ (mmHg)	80 (70–90)
Body mass index‡	21.6 (20.9–22.9)

* Drinking: ever-drinking alcoholic beverages in the last 12 months.
† Smoking: liferime use of cigarettes for ≥6 months.
‡ Median (interquartile range).

receiving each of the four nutrient combinations, with subjects who received and did not receive a given factor balanced with respect to all of the other nutrients. Supplementation delivery occurred monthly, beginning in March 1986 and continuing through April 1991. To assess compliance, we counted unused pills and assayed nutrient levels in blood collected from random samples of participants every 3 months.

The ascertainment of all deaths and all incident cancers in trial participants occurred through routine and special follow-up that ensured essentially complete reporting. Local physicians determined the cause of noncancer deaths, including stroke. Experienced senior Chinese clinicians involved in this study reviewed these decisions. At baseline (before randomization) in 1985 and again in the spring of 1991, we administered questionnaires and conducted brief physical examinations. The questionnaire elicited information on age, sex, cigarette smoking, and alcohol drinking. Physical examinations included standard mercury sphygmomanometer measurement of systolic and diastolic blood pressure and measurement of weight and height. In 1991, 77% of the surviving trial participants had their blood pressures measured by field staff blinded to intervention group status. The rate of ascertainment of blood pressure did not differ by treatment group. At both the baseline and end-of-trial examinations, the blood pressures were taken once at the beginning of the physical examination with the subject seated. At the end of the trial, participants were classified as being either "healthy" or in one of the following categories: (1) dead from stroke; (2) dead from other causes; (3) alive with cancer; (4) alive, cancer free, with systolic (systolic pressure ≥160 mmHg) but not diastolic hypertension; (5) alive, cancer free, with diastolic (diastolic pressure ≥95 mmHg) but not systolic hypertension; (6) alive, cancer free, with both systolic and diastolic hypertension. The cutoff values for systolic and diastolic pressure follow World Health Organization criteria.[5]

Using proportional hazards models,[6] we estimated the relative risks (RR) and corresponding 95% confidence intervals (CI) for the effect of treatment and baseline risk factors on stroke mortality. To examine the proportionality assumption, we used graphical display and time-dependent models that tested for variation of the relative risk over time. Since adjustment for baseline risk factors resulted in essentially no change in estimates of the treatment effect on overall mortality, cancer mortality, or stroke mortality, we present the unadjusted estimates. We present RRs based on two separate analyses. Our primary analysis concerns RRs associated with the four treatment factors, A, B, C, and D. The analysis by factor imposes the simplifying assumption that the effects of the factors are additive on a log scale. Even though the experiment gives little evidence that contradicts this assumption ($P = 0.29$ by likelihood ratio test), we also present the RR estimates for each of the individual randomization groups. These RRs provide the relative risk of stroke for each of the seven groups that received some active supplement compared to the single group that received placebo. We used linear regression to estimate the effect of the treatment on 1991 systolic and diastolic blood pressure. Polytomous logistic regression[7] was used to compare the odds in the treated *vs* the nontreated group for each of the six possible disease categories. This analysis displays the effect of the treatments on mutually exclusive and exhaustive disease categories without making any assumptions about the dependencies between these disease categories and shows exactly how the treatments affected the distribution of disease states at the end of the trial. To decrease the potential bias that arises from the lack of blood pressure measurements at the end of the study on 23% of the eligible individuals, the linear regression and polytomous logistic regression models include terms for baseline covariates. In all models with continuous covariates as predictors, piecewise polynomial models with and without quadratic terms were tested to see whether model fit improved.

Results

Table 2 shows characteristics of the participants at the start of the trial. Fifty-five per cent of the participants were female. The median age was 2 years less for women

TABLE 3. Numbers, Rates, and Relative Risks of All Deaths and Stroke Deaths by Randomization Group and by Treatment Factor

		All Deaths			Stroke Deaths				
							RR (95% CI)		
	Person-Years	No.	Rate per 1,000 Person-Years	RR (95% CI)	No.	Rate per 1,000 Person-Years	Total	Women	Men
Group									
Placebo	18,626	280	15.0		77	4.1			
AB	18,736	265	14.1	0.94 (0.79–1.11)	66	3.5	0.85 (0.61–1.18)	0.86 (0.53–1.39)	0.85 (0.54–1.33)
AC	18,701	296	15.8	1.05 (0.89–1.24)	71	3.8	0.91 (0.66–1.27)	0.83 (0.51–1.35)	0.99 (0.64–1.53)
AD	18,745	250	13.3	0.89 (0.75–1.05)	55	2.9	0.71 (0.50–1.00)	0.72 (0.43–1.19)	0.70 (0.43–1.11)
BC	18,686	268	14.3	0.95 (0.81–1.13)	60	3.2	0.78 (0.55–1.09)	0.81 (0.49–1.32)	0.75 (0.47–1.19)
BD	18,729	263	14.0	0.93 (0.79–1.11)	58	3.1	0.75 (0.53–1.05)	0.83 (0.50–1.35)	0.68 (0.41–1.08)
CD	18,758	249	13.2	0.88 (0.74–1.05)	67	3.6	0.86 (0.62–1.20)	0.86 (0.53–1.39)	0.87 (0.55–1.35)
ABCD	18,792	256	13.6	0.91 (0.76–1.07)	69	3.7	0.88 (0.64–1.22)	0.89 (0.55–1.43)	0.89 (0.57–1.38)
Factor*									
A				1.00 (0.92–1.09)			0.99 (0.84–1.18)	0.94 (0.73–1.21)	1.04 (0.82–1.32)
B				0.98 (0.90–1.06)			0.94 (0.79–1.11)	0.99 (0.77–1.27)	0.89 (0.70–1.12)
C				1.01 (0.92–1.10)			1.04 (0.88–1.24)	0.99 (0.77–1.28)	1.09 (0.86–1.37)
D				0.91 (0.84–0.99)			0.91 (0.84–0.99)	0.94 (0.73–1.21)	0.87 (0.69–1.10)

* A = retinol, zinc; B = riboflavin, niacin; C = ascorbic acid, molybdenum; D = beta-carotene, alpha-tocopherol, selenium.

(51 years) than men (53 years). About two-thirds of the men, but few women, smoked cigarettes (that is, lifetime use for 6 months or more). Ten per cent of the women reported ever drinking alcoholic beverages in the past year, compared with 40% of the men. Drinking was typically infrequent and in small amounts: over 90% of persons classified as drinkers reported drinking only a few times a year, with most of the remaining reporting drinking a few times per month. Median blood pressure was 130/80 among women and 120/80 among men. The eight treatment groups were well balanced with respect to all of the baseline characteristics, including both systolic and diastolic blood pressure, and the serum nutrient levels examined.[4]

Data on serum nutrients from samples of trial participants, and from surveys before the start of the trial, indicate that the Linxian region has poor overall nutrition. In dietary surveys in this area, we have found that as many as 90% of adults have less than two-thirds the Chinese or U.S. recommended intake of vitamin A, riboflavin, and calcium.[8] Plasma levels of retinol, many of the carotenoids, alpha-tocopherol, ascorbic acid, riboflavin, and zinc have also been low compared with levels in the U.S. population.[3,9,10]

During the 5-year course of the study 2,127 deaths (rate = 14.2 per 1,000 person-years), including 792 cancer deaths (rate = 5.3 per 1,000 person-years) and 523 stroke deaths (rate = 3.5 per 1,000 person-years), occurred. We have previously reported death frequency by cause of death and by group.[4] Table 3 shows the effects of treatment factor and treatment group on overall mortality and stroke mortality. The largest risk reduction in overall mortality, 9%, was experienced by individuals taking factor D (RR = 0.91; 95% CI = 0.84–0.99). Sex did not modify the effects of the treatment factors[11] or groups (data not shown) on overall mortality.

Individuals receiving factor D also experienced the lowest stroke mortality (RR = 0.91; 95% CI = 0.76–1.07). Compared with the group that received placebo, a modest benefit occurred in all seven of the randomization groups that received nutritional supplements, with the largest reduction in the AD group (RR = 0.71; 95% CI = 0.50–1.00). Those receiving AD along with BC (that is, group ABCD) did not have a correspondingly low RR. The effect of sex (right two columns of Table 3) on the variation by group or factor was small.

Individuals age 60 years or more with systolic hypertension (systolic pressure ≥160) at baseline accounted for approximately 7% of the study population but experienced 36% of the stroke deaths. For most of the factors and groups, the treatment effects tended not to differ by risk level as defined by age and systolic hypertension criteria. Nevertheless, in the two groups that received both factors A and B (that is, groups AB and ABCD), the supplemented high-risk individuals had lower stroke mortality. For the AB group, the relative risk was 1.23 (95% CI = 0.81–1.85) for low-risk and 0.47 (95% CI = 0.26–0.86) for high-risk individuals. For the ABCD group, the relative risk was 1.18 (95% CI = 0.78–1.79) for low-risk and 0.53 (95% CI = 0.30–0.94) for high-risk individuals.

The death rate from stroke in men (adjusted for smoking and drinking) was 70% greater than the rate among women (RR = 1.7; 95% CI = 1.32–2.12). Table 4 lists

TABLE 4. Relative Risk of Stroke Associated with Pretreatment Variables (Linxian, China, 1985–1991)

	RR*	95% CI
Systolic blood pressure per 5 mmHg	1.12	1.09–1.15
Diastolic blood pressure per 5 mmHg	1.12	1.07–1.16
Age per 5 years	1.51	1.42–1.61
Body mass index† per 1.5 units	1.02	0.97–1.07
Alcohol drinking	0.77	0.61–0.98
Smoking	1.09	0.85–1.40

* Estimates when all pretreatment variables are entered simultaneously into a Cox model stratified on sex.
† Units chosen to approximate the interquartile range.

TABLE 5. Effect (in mmHg) of Treatment Factor and Randomization Group on End of Study Blood Pressure, from Linear Regression Analysis. Model Includes Terms for Age, Baseline Systolic Blood Pressure (SBP), Baseline Diastolic Blood Pressure (DBP), Smoking, Drinking, and Body Mass Index. 95% Confidence Limits in Parentheses

	Treatment Factor			
	A	B	C	D
SBP	0.67 (0.07, 1.25)	−0.57 (−1.17, 0.02)	−0.50 (−1.09, 0.09)	0.00 (−0.59, 0.60)
DBP	0.29 (−0.07, 0.65)	−0.37 (−0.73, −0.02)	−0.24 (−0.60, 0.12)	0.26 (−0.09, 0.62)

	Randomization Group						
	CD	AC	BD	AB	BC	AD	ABCD
SBP	−0.67 (−1.85, 0.51)	0.40 (−0.79, 1.58)	−0.33 (−1.52, 0.86)	−0.08 (−1.28, 1.10)	−1.17 (−2.36, 0.01)	0.56 (−0.62, 1.74)	−0.41 (−1.59, 0.77)
DBP	−0.21 (−0.92, 0.50)	0.04 (−0.67, 0.76)	−0.12 (−0.84, 0.60)	−0.32 (−1.04, 0.40)	−0.96 (−1.68, −0.25)	0.21 (−0.51, 0.92)	−0.06 (−0.77, 0.65)

the relative risks (controlling for sex) of stroke mortality associated with other pretreatment variables. The important predictors of elevated stroke risk were increasing age (RR = 1.51 for every 5-year increase), increasing systolic blood pressure (RR = 1.12 for each 5 mmHg), and increasing diastolic pressure (RR = 1.12 for each 5 mmHg). A decreased stroke risk was found among those with a history of alcohol consumption, with drinkers experiencing a 23% lower rate of strokes than nondrinkers (RR = 0.77; 95% CI = 0.61–0.98).

Table 5 shows treatment effects on the end of study systolic and diastolic blood pressures. The magnitude of these effects was small. A history of alcohol drinking also had only small effects on either systolic (average decrease of 0.59 mmHg) or diastolic pressures (average increase of 0.14 mmHg).

Table 6 presents the effect of the interventions on the mutually exclusive and exhaustive outcome categories of stroke mortality, other causes of death, hypertension, and nonfatal cancers. This table displays the overall effect of each intervention on the health of the subjects who received it. Analyzing by factors, only factor D had an important impact on these categorical outcomes (Table 6). This effect was largely due to a reduction in nonstroke mortality (RR = 0.90; 95% CI = 0.81–1.00) and stroke mortality (RR = 0.89; 95% CI = 0.74–1.08) and to an increased prevalence of isolated diastolic hypertension (RR = 1.23; 95% CI = 1.06–1.43). For

TABLE 6. Rate Ratios for Effect of Factor and Treatment Group on End-of-Trial Outcomes from Polytomous Regression. Model Includes Terms for Age, Baseline Systolic Blood Pressure, Baseline Diastolic Blood Pressure, Smoking, Drinking, and Body Mass Index. The Reference Category Is Those Who Are Alive and Free of Cancer, Systolic Hypertension, and Diastolic Hypertension

	High Systolic	High Diastolic	High Both	Alive with Cancer	Stroke Death	Other Death
Treatment factor						
A	1.07 (0.96–1.21)	1.13 (0.98–1.31)	1.05 (0.94–1.18)	1.05 (0.89–1.26)	1.06 (0.88–1.28)	1.04 (0.94–1.16)
B	0.95 (0.85–1.08)	0.84 (0.73–0.98)	1.05 (0.94–1.18)	0.91 (0.76–1.08)	0.97 (0.81–1.17)	0.99 (0.89–1.10)
C	0.94 (0.84–1.07)	0.95 (0.82–1.10)	0.89 (0.79–0.99)	1.03 (0.87–1.24)	0.99 (0.82–1.19)	0.97 (0.87–1.08)
D	0.93 (0.83–1.05)	1.23 (1.06–1.42)	0.98 (0.87–1.09)	1.01 (0.85–1.21)	0.89 (0.74–1.08)	0.90 (0.81–1.00)
Treatment group						
CD	0.93 (0.73–1.19)	1.13 (0.86–1.50)	0.85 (0.67–1.06)	1.18 (0.83–1.70)	0.86 (0.60–1.22)	0.88 (0.71–1.09)
AC	1.11 (0.88–1.41)	0.94 (0.70–1.26)	0.93 (0.74–1.16)	1.27 (0.88–1.81)	1.00 (0.71–1.42)	1.17 (0.95–1.44)
BD	0.98 (0.77–1.25)	0.90 (0.67–1.22)	1.03 (0.82–1.28)	1.07 (0.74–1.55)	0.83 (0.58–1.20)	1.03 (0.84–1.28)
AB	1.08 (0.85–1.38)	0.94 (0.70–1.26)	1.08 (0.87–1.35)	1.06 (0.73–1.55)	1.00 (0.70–1.43)	1.03 (0.84–1.28)
BC	0.96 (0.76–1.22)	0.68 (0.50–0.94)	0.92 (0.74–1.15)	1.18 (0.82–1.70)	0.76 (0.53–1.10)	1.00 (0.82–1.25)
AD	1.07 (0.85–1.36)	1.23 (0.93–1.62)	1.01 (0.81–1.26)	1.33 (0.94–1.90)	0.75 (0.51–1.08)	0.99 (0.80–1.22)
ABCD	0.91 (0.71–1.16)	1.10 (0.84–1.47)	0.97 (0.77–1.20)	1.01 (0.70–1.47)	0.92 (0.65–1.31)	0.90 (0.73–1.19)

factor C, there was a decreased prevalence for all three categories of hypertension. Of the treatment groups, BC group was the only one with a consistent direction of effect (decreased prevalence) for all three categories of hypertension and death from stroke. None of the other treatments affected the overall distribution of outcomes appreciably (Table 6).

Discussion

The causes of hypertension and stroke are complex and largely unknown. With the exception of the well-established relation between hypertension and stroke, little is understood about other potentially modifiable risk factors for either disease. Ecologic studies,[12–18] migrant studies,[19] observational analyses of assembled cohorts,[12,20–24] and (for hypertension, at least) intervention trials[13,25,26] have indicated that diet may be important in influencing the risk of these diseases. Best established is the association between elevated blood pressure and high dietary sodium consumption or sodium-to-potassium ratio. Two recent small randomized trials evaluating vitamin C noted decreases in blood pressure after 4 and 6 weeks of daily supplementation,[27,28] consistent with observational studies linking decreased blood pressure with higher levels of vitamin C intake. The dose of vitamin C in these trials was more than twice as high as the dose in our General Population Trial.

Only a few analytical studies have evaluated risk of stroke in relation to dietary nutrients. One of the earliest reported a beneficial effect of potassium consumption, itself highly correlated with intake of fruits and vegetables.[22] Subsequent studies have suggested protective effects of antioxidants and serum beta-carotene.[29–32] Studies evaluating the intake of vitamins C and E have reported either protective effects or null effects.[31–37] A small clinical trial of secondary stroke prevention that compared aspirin *vs* aspirin and vitamin E[38] noted a lower incidence of stroke with vitamin E supplements, but the rapidity of the effect indicated an antiadhesive action on platelets rather than an antioxidant mechanism. Flavonoids, nonnutritive components of plant foods with antioxidant properties, have recently been suggested as protective against stroke.[29] More detailed reviews have summarized evidence on the relation of micronutrients to hypertension and stroke,[2] and to cardiovascular disease in general.[39]

In addition to the present trial, only two randomized studies of vitamin intervention have evaluated stroke mortality as a separate category. The Alpha-Tocopherol Beta-Carotene Intervention Trial,[40] a two-by-two factorial study of middle-aged male cigarette smokers in Finland, observed slightly higher rates of stroke mortality in both the vitamin E and the beta-carotene groups than in the controls. Combining the reported categories of hemorrhagic and ischemic stroke, and assuming that the number of deaths follow a Poisson distribution, we calculate the relative risks of stroke mortality to be 1.10 (95% CI = 0.85–1.42) for the vitamin E recipients and 1.21 (95% CI = 0.93–1.56) for the beta-carotene recipients in the Finnish trial. No measure of blood pressure was reported. The Linxian Dysplasia Trial,[2,41] conducted as a companion to our general population study, is discussed below.

In the present study, whose participants consumed low quantities of many important micronutrients in their diet, individuals were randomly assigned either to a placebo group or to one of seven other groups. Each of these seven groups received different combinations of nutrient supplements and showed some lowering of stroke mortality. These reductions ranged from 29% (the group that received vitamin A, zinc, beta-carotene, selenium, and alpha-tocopherol) to 9% (the group that received vitamin A, zinc, molybdenum, and vitamin C). The precision of the individual estimates (as measured by their confidence intervals) is not sufficient to conclude that the agents in one treatment group are superior to those in another group or, for that matter, to placebo. Furthermore, since all seven supplemented groups were compared with the same placebo group, and there is a 1 in 8 chance that the placebo group will have the highest rate of stroke death even when no benefit of nutritional supplementation exists, the "consistent" beneficial effect we found is not strong evidence for the merits of nutritional supplementation in this population. It is of note that both treatment groups receiving the combination of vitamin A, zinc, riboflavin, and thiamine (AB, ABCD) showed a beneficial effect on stroke for high-risk subjects (age $\geq$60 years, systolic blood pressure $\geq$160) but not for others.

Whereas the design of this study enables us to compare differences in outcomes between the seven supplemented groups and the placebo group, the primary intent of this study was to evaluate the effects of the four treatment factors A, B, C, and D. The factors themselves are a combination of several nutrients, aggregated according to their underlying biochemical mechanisms of action.[4] Using as an outcome the disease categories in Table 6, only the lipid-soluble antioxidants (factor D) had a measurable impact on stroke mortality, as well as on other causes of death. For the other three factors, there was no clear-cut evidence for an effect on stroke or other causes of death (predominantly cancer). Factor C (vitamin C and molybdenum) had a small beneficial effect on all categories of hypertension, and on average systolic and diastolic blood pressure.

Contemporaneously with this General Population Trial and its factorial design, we conducted another, smaller trial in Linxian, the Dysplasia Trial, in which subjects with esophageal dysplasia received either a placebo or multivitamin/mineral preparation.[2,41] With the exception of being slightly older (median age higher by 2 years), and having a precursor lesion to esophageal cancer, the participants of the two trials were similar. The overall stroke mortality rate in the Dysplasia Trial (3 per 1,000 person-years)[2] was comparable with that in the General Population Trial (3.5 per 1,000 person-years). The supplemented group in the Dysplasia Trial, however, had a reduction in stroke mortality rate that surpassed the benefit noted in any of the general popu-

lation groups. In addition, whereas the general population study showed no evident sex difference in the effect of supplements, the benefit in the Dysplasia Trial was far greater in men (RR = 0.42; 95% CI = 0.19–0.93) than women (RR = 0.93; 95% CI = 0.44–1.98). Similarly, the lowered prevalence of both systolic and diastolic hypertension after supplement use in the Dysplasia Trial was more pronounced in men.[2]

The multivitamin/minerals given in the Dysplasia Trial contained the nine nutrients used in the general population study, plus 10 other mineral compounds and seven other vitamins (six water-soluble vitamins and vitamin D). Although the different treatment effects on stroke mortality found in the two trials could result from any number of factors, one possible explanation is the varied composition of the supplements. In particular, it is possible that the B vitamins folate, pyridoxine, and cyanocobalamine (B_{12}), given only in the Dysplasia Trial, contributed to the reduction in stroke mortality and, possibly, hypertension. All three of these B vitamins are important cofactors in the metabolism of homocysteine, and supplementation with these vitamins, particularly folate, has been shown to lower homocysteine levels.[42,43] There is growing evidence linking elevated serum (or plasma) levels of total homocysteine and decreased serum levels and/or intake of folate, pyridoxine, or B_{12}, with arterial occlusive disease[42–44] in general, and with stroke in particular.[45–48] In the populations examined to date, homocysteine levels have been approximately 20% higher in men than in women,[42] which may help explain the greater treatment benefit among men in the Dysplasia Trial.

The supplemented individuals in the Dysplasia Trial also received higher doses of potassium, calcium, and magnesium. All of these cations have been suggested as exerting beneficial effects on blood pressure.[21–23,25]

The relations we observed between stroke risk and male sex, increasing age, and increasing systolic or diastolic blood pressure are well established. The association of smoking with stroke in our study (RR = 1.09; 95% CI = 0.85–1.40) was not as strong as that reported in a recent meta-analysis (RR = 1.5; 95% CI = 1.45–1.58).[49] The smokers in our study population, however, would generally be classified as "light" smokers, with a median of 11 pack-years. Of special interest is the apparent protective effect associated with alcohol drinking in our study, since some studies have suggested an increased risk of stroke with heavy drinking, and of hemorrhagic stroke with all levels of drinking.[50,51] For ischemic and overall stroke, however, there is limited evidence that low or moderate levels of drinking may be associated with reduced risk.[51] In the Linxian studies, we could not distinguish hemorrhagic from ischemic stroke, but population statistics in China indicate that approximately two-thirds of the strokes are ischemic.[52] Those who consumed alcohol in Linxian tended to be light or infrequent drinkers, and they showed risk reductions of 23%. Whether this effect is due to a low level of alcohol consumption or some other unmeasured trait correlated with alcohol intake or abstention is unknown.

By continued follow-up of these study populations, and from the analyses of the biological specimens collected, it should be possible to characterize further the effects of the interventions. We are presently conducting a nested case-cohort study to explore the associations between serum vitamin and homocysteine levels with the occurrence of stroke in the General Population and Dysplasia Trials, and to investigate whether the risks vary by the treatment received.

References

1. Blot WJ, Li JY. Some considerations in the design of a nutrition intervention trial in Linxian, People's Republic of China. Natl Cancer Inst Monogr 1985;69:29–34.
2. Mark SD, Wang W, Fraumeni JF Jr, Li JY, Taylor PR, Wang GQ, Guo W, Dawsey SM, Li B, Blot WJ. Lowered risks of hypertension and cerebrovascular disease following vitamin/mineral supplementation: results from the Linxian Intervention Trials. Am J Epidemiol 1996;143:658–664.
3. Li B, Taylor PR, Li JY, Dawsey SM, Wang W, Tangrea JA, Liu BQ, Ershow AG, Zheng SF, Fraumeni JF Jr, Yang Q, Yu Y, Sun Y, Li G, Zhang D, Greenwald P, Lian GT, Yang CS, Blot WJ. Linxian nutrition intervention trial: design, methods, participant characteristics, and compliance. Ann Epidemiol 1993;3:577–585.
4. Blot WJ, Li JY, Taylor PR, Guo W, Dawsey S, Wang GQ, Yang CS, Zheng SF, Gail M, Li GY, Yu Y, Liu BQ, Tangrea J, Sun YH, Liu F, Fraumeni JF Jr, Zhang YH, Li B. Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. J Natl Cancer Inst 1993;85:1483–1492.
5. Zanchetti A, Chalmers JP, Arakawa K, Gyarfas I, Hamet P, Hansson L, Julius S, MacMahon S, Mancia G, Menard J. 1993 guidelines for the management of mild hypertension: memorandum from a WHO/ISH meeting. Bull World Health Organ 1993;71:507–517.
6. Cox DR. Regression models and life tables (with discussion). J R Stat Soc B 1972;34:187–220.
7. Agresti A, ed. Categorical Data Analysis. New York: John Wiley and Sons, 1990.
8. Ershow AG, Zheng SF, Li GY, Li JY, Yang CS, Blot WJ. Compliance and nutritional status during feasibility study for an intervention trial in China. J Natl Cancer Inst 1984;73:1477–1481.
9. Yang CS, Sun YH, Yang QP, Miller KW, Li GY, Zheng SF, Ershow AG, Li JY, Blot WJ. Nutritional status of the high esophageal cancer risk population in Linxian, People's Republic of China: effects of vitamin supplementation. Natl Cancer Inst Monogr 1985;69:23–27.
10. Yang CS, Sun Y, Yang QU, Miller KW, Li GY, Zheng SF, Ershow AG, Blot WJ, Li JY. Vitamin A and other deficiencies in Linxian, a high esophageal cancer incidence area in northern China. J Natl Cancer Inst 1984;73:1449–1453.
11. Blot WJ, Li JY, Taylor PR, Guo W, Dawsey SM, Li B. The Linxian trials: mortality rates by vitamin-mineral intervention group. Am J Clin Nutr 1995;62:1424S–1426S.
12. Elliott P. Observational studies of salt and blood pressure. Hypertension 1991;17:13–18.
13. Maxwell MH, Waks AU. Cations and hypertension: sodium, potassium, calcium, and magnesium. Med Clin North Am 1987;71:859–875.
14. Klag MJ, Whelton PK, Seidler AJ. Decline in US stroke mortality: demographic trends and antihypertensive treatment. Stroke 1989;20:14–21.
15. Klag MJ, Whelton PK. Stroke and nutrition: a review. Clin Nutr 1989;8:34–41.
16. Higgins M, Thom T. Trends in stroke risk factors in the United States. Ann Epidemiol 1993;3:550–554.
17. Thom TJ. Stroke mortality trends: an international perspective. Ann Epidemiol 1993;3:509–518.
18. Acheson RM, Williams DR. Does consumption of fruit and vegetables protect against stroke? Lancet 1983;1:1191–1193.
19. Stamler J. The Yi Migrant Study: population exposures influencing blood pressure patterns. Epidemiology 1991;2:83–87.
20. Berlin LJ. Vegetarian and other complex diets, fats, fiber and hypertension. Am J Clin Nutr 1994;59:1130S–1135S.
21. Klag MJ, Whelton PK. The decline in stroke mortality: an epidemiologic perspective. Ann Epidemiol 1993;3:571–575.
22. Khaw KT, Barrett-Connor E. Dietary potassium and stroke-associated mortality: a 12-year prospective population study. N Engl J Med 1987;316:235–240.
23. Ascherio A, Rimm EB, Giovannucci EL, Colditz GA, Rosner B, Willett WC, Sacks F, Stampfer MJ. A prospective study of nutritional factors and hypertension among US men. Circulation 1992;86:1475–1484.

24. McCarron DA, Morris CD, Henry HJ, Stanton JL. Blood pressure and nutrient intake in the United States. Science 1984;224:1392–1398.
25. Cappuccio FP, MacGregor GA. Does potassium supplementation lower blood pressure? A meta-analysis of published trials. J Hypertens 1991;9:465–473.
26. Bucher HC, Cook DJ, Guyatt GH, Lang JD, Cook DJ, Hatala R, Hunt DL. Effects of dietary calcium supplementation on blood pressure: a meta-analysis of randomized controlled trials. JAMA 1996;275:1016–1022.
27. Lovat LB, Lu Y, Palmer AJ, Edwards R, Fletcher AE, Bulpitt CJ. Double-blind trial of vitamin C in elderly hypertensives. J Hum Hypertens 1993;7:403–405.
28. Ghosh SK, Ekpo EB, Shah IU, Girling AJ, Jenkins C, Sinclair AJ. A double-blind, placebo-controlled parallel trial of vitamin C treatment in elderly patients with hypertension. Gerontology 1994;40:268–272.
29. Keli SO, Hertog MG, Feskens EJ, Kromhout D. Dietary flavonoids, antioxidant vitamins, and incidence of stroke: the Zutphen study. Arch Intern Med 1996;156:637–642.
30. Virtamo J, Valkeila E, Alfthan G, Punsar S, Huttunen JK, Karvonen MJ. Serum selenium and the risk of coronary heart disease and stroke. Am J Epidemiol 1985;122:276–282.
31. Kok FJ, de Bruijn AM, Vermeeren R, Hofman A, van Laar A, de Bruin M, Hermus RJ, Valkenburg HA. Serum selenium, vitamin antioxidants, and cardiovascular mortality: a 9-year follow-up study in the Netherlands. Am J Clin Nutr 1987;45:462–468.
32. Gey KF, Stähelin HB, Eichholzer M. Poor plasma status of carotene and vitamin C is associated with higher mortality from ischemic heart disease and stroke: Basel Prospective Study. Clin Invest 1993;71:3–6.
33. Vollset SE, Bjelke E. Does consumption of fruit and vegetables protect against stroke? Lancet 1983;2:742.
34. Lapidus L, Andersson H, Bengtsson C, Bosaeus I. Dietary habits in relation to incidence of cardiovascular disease and death in women: a 12-year follow-up of participants in the population study of women in Gothenburg, Sweden. Am J Clin Nutr 1986;44:444–448.
35. Barer D, Leibowitz R, Ebrahim S, Pengally D, Neale R. Vitamin C status and other nutritional indices in patients with stroke and other acute illnesses: a case-control study. J Clin Epidemiol 1989;42:625–631.
36. De Keyser J, De Klippel N, Merkx H, Vervaeck M, Herroelen L. Serum concentrations of vitamins A and E and early outcome after ischaemic stroke. Lancet 1992;339:1562–1565.
37. Stampfer MJ, Hennekens CH, Manson JE, Colditz GA, Rosner B, Willett WC. Vitamin E consumption and the risk of coronary disease in women. N Engl J Med 1993;328:1444–1449.
38. Steiner M, Glantz M, Lekos A. Vitamin E plus aspirin compared with aspirin alone in patients with transient ischemic attacks. Am J Clin Nutr 1995;62:1381s–1384s.
39. Jha P, Flather M, Lonn E. The antioxidant vitamins and cardiovascular disease: a critical review of the epidemiologic and clinical trial data. Ann Intern Med 1995;123:860–872.
40. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study Group. The effect of vitamin E and beta-carotene on the incidence of lung cancer and other cancers in male smokers. N Engl J Med 1994;330:1029–1035.
41. Li JY, Taylor PR, Li B, Dawsey S, Wang GQ, Ershow AG, Guo W, Liu SF, Yang CS, Shen Q, Wang W, Mark SD, Zou XN, Greenwald P, Wu YP, Blot WJ. Nutrition intervention trials in Linxian, China: multiple vitamin/mineral supplementation, cancer incidence, and disease-specific mortality among adults with esophageal dysplasia. J Natl Cancer Inst 1993;85:1492–1498.
42. Malinow MR. Homocyst(e)ine and arterial occlusive diseases. J Intern Med 1994;236:603–617.
43. Boushey CJ, Beresford SA, Omenn GS, Motulsky AG. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease: probable benefits of increasing folic acid intakes. JAMA 1995;274:1049–1057.
44. Selhub J, Jacques PF, Bostom AG, D'Agostino RB, Wilson PW, Belanger AJ, O'Leary DH, Wolf PA, Schaefer EJ, Rosenberg IH. Association between plasma homocysteine concentrations and extracranial carotid-artery stenosis. N Engl J Med 1995;332:286–291.
45. Giles WH, Kittner SJ, Anda RF, Croft JB, Casper ML. Serum folate and risk for ischemic stroke. First National Health and Nutrition Examination Survey epidemiologic follow-up study. Stroke 1995;26:1166–1170.
46. Perry IJ, Refsum H, Morris RW, Ebrahim SB, Ueland PM, Shaper AG. Prospective study of serum total homocysteine concentration and risk of stroke in middle-aged British men. Lancet 1995;346:1395–1398.
47. Verhoef P, Hennekens CH, Malinow MR, Kok FJ, Willett WC, Stampfer MJ. A prospective study of plasma homocyst(e)ine and risk of ischemic stroke. Stroke 1994;25:1924–1930.
48. Alfthan G, Pekkanen J, Jauhiainen M, Pitkaniemi J, Karvonen M, Tuomilehto J, Salonen JT, Ehnholm C. Relation of serum homocysteine and lipoprotein(a) concentrations to atherosclerotic disease in a prospective Finnish population based study. Atherosclerosis 1994;106:9–19.
49. Shinton R, Beevers G. Meta-analysis of relation between cigarette smoking and stroke. BMJ 1989;298:789–794.
50. Bronner LL, Kanter DS, Manson JE. Primary prevention of stroke. N Engl J Med 1995;333:1392–1400.
51. Van Gijn J, Stampfer MJ, Wolfe C, Algra A. The association between alcohol and stroke. In: Verschuren PM, ed. Health Issues Related to Alcohol Consumption. Washington DC: ILSI Press, 1993;43–79.
52. Shi FL, Hart RG, Sherman DG, Tegeler CH. Stroke in the People's Republic of China. Stroke 1989;20:1581–1585.